

REMARKS

I. Status Summary

Claims 1-79 are pending in the present U.S. patent application. Claims 18-79 were withdrawn from consideration as being directed to unelected subject matter and have now been canceled without prejudice herein. Claims 1-17 are pending and have been examined.

Claim 4 has been rejected under 35 U.S.C. § 112, second paragraph, upon the contention that the claim recites a polypeptide while the claim on which it depends, claim 3, recites a nucleic acid.

Claims 1-3 and 16-17 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Flattem et al. (Am. J. Human Genetics, Vol. 65, No. 4, p. A43, 1999; also referred to herein as the "Flattem Abstract"). Claims 1, 3, 6-7, 13, and 17 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Jonsson et al. (Psychiatry Research, Vol. 79, pp. 1-9, 1998; also referred to herein as "Jonsson").

Claim 2 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Jonsson in view of Jacob et al. (Circulation, Vol. 99, pp. 1706-12, 1999; also referred to herein as "Jacob"). Claims 11-12 and 16 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Jonsson in view of Pesonen et al. (U.S. Patent No. 6,013,449; also referred to herein as "Pesonen"). Claims 9-10 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Jonsson in view of Weimer et al. (U.S. Patent No. 6,248,526; also referred to herein as "Weimer").

Claims 4-5, 8, and 14-15 are objected to as being dependent upon a rejected base claim. The United States Patent and Trademark Office (hereinafter the "Patent Office") has indicated that these claims are free of the art and are allowable if rewritten in independent form including all of the elements of the base claim and any intervening claims.

Claims 4, 5, 8, 14, and 15 have been amended. The amendments to these claims include amending previously dependent claims into independent form, including all the elements of the base claims and any intervening claims. Thus, support for the amendments can be found in the claims as originally filed. These amendments do not

introduce any new matter. Reconsideration of the application as amended and based on the arguments sets forth herein below is respectfully requested.

II. *Claim Rejections under 35 U.S.C. § 112, Second Paragraph*

Claim 4 has been rejected under 35 U.S.C. § 112, second paragraph, upon the contention that the claim recites a polypeptide while the claim on which it depends, claim 3, recites a nucleic acid. According to the Patent Office, there is insufficient antecedent basis for the term "the NE transporter polypeptide" in claim 4. Claim 4 has been amended to replace "polypeptide" with "gene". Support for the amendment can be found throughout the specification, for example, on page 6, lines 21-22, and page 12, lines 6-8. Applicants respectfully submit that as a result of the amendment, claim 4 is now in condition for allowance and respectfully request a Notice of Allowance to that effect.

III. *Claim Rejections under 35 U.S.C. § 102*

III.A. *Rejection Based upon the Flattem Abstract*

Claims 1-3 and 16-17 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Flattem *et al.* (Am. J. Human Genetics, Vol. 65, No. 4, p. A43, 1999; hereinafter "the Flattem Abstract"). According to the Patent Office:

Flattem *et al.* teach a method for screening for susceptibility to norepinephrine (NE) transporter [defects] wherein... the method comprises (a) obtaining a biological sample from a human subject (proband) and detecting a polymorphism (mutation) of a norepinephrine (NE) transporter in the biological sample from the subject and detecting the presence of the polymorphism (mutation) as an indication of the susceptibility of the subject to sub-optimal NE transport in orthostatic intolerance.

Official Action, pages 2-3. After careful consideration of the rejection and the Patent Office's basis for the rejection, applicants respectfully traverse the rejection and offer the following comments.

That Patent Office contends that the Flattem Abstract qualifies as 102(b) prior art in the instant application. Applicants respectfully point out that in order to qualify as

102(b) prior art, a reference must be available to the public more than one year prior to the filing of a United States patent application. The instant application claim priority to U.S. Provisional Application Serial Number 60/173,682, which was filed December 29, 1999. The Flattem Abstract appeared in the October 1999 issue of the American Journal of Human Genetics. As such, applicants respectfully submit that the Flattem Abstract does not qualify as 102(b) prior art. Accordingly, applicants respectfully request that the rejection of claims 1-3 and 16-17 under 35 U.S.C. § 102(b) be withdrawn and the claims be allowed at this time.

However, in an abundance of caution, applicants submit the following in case the Patent Office had intended the current rejection to be based upon 35 U.S.C. § 102(a) instead of 102(b). 35 U.S.C. § 102(a) requires that the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent. 35 U.S.C. § 102(a) (emphasis added). In response to the 35 U.S.C. § 102(a) rejection, applicants respectfully submit the attached Declaration under 37 CFR §1.131 regarding the Flattem Abstract. Summarily, the attached Declaration establishes that the inventive subject matter of claims 1-3 and 16-17 was invented prior to the publication date of the Flattem Abstract. Consequently, it is respectfully submitted that the rejection of claims 1-3 and 16-17 under 35 U.S.C. § 102(a) as being anticipated by the Flattem Abstract has now been addressed. It is therefore respectfully requested that the Flattem Abstract be withdrawn as a reference, and hence, that the rejections be withdrawn and the claims allowed at this time.

III.B. Rejection Based upon the Jonsson Journal Article

Claims 1, 3, 6-7, 13, and 17 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Jonsson *et al.* (Psychiatry Research, Vol. 79, pp. 1-9, 1998; hereinafter "Jonsson"). According to the Patent Office:

Jonsson *et al.* teach a method for screening for susceptibility to norepinephrine (NE) transport [defects] in a human subject wherein... the method comprises (a) obtaining a biological sample from a human subject (proband) and detecting a polymorphism (mutation) of a norepinephrine

(NE) transporter in the biological sample from the subject and detecting the presence of the polymorphism (mutation) as an indication of the susceptibility of the subject to a sub-optimal NE transport. Jonsson also teaches that the method comprises (i) biological sample comprising nucleic acid; (ii) detection of polymorphism by amplifying the target nucleic acid using PCR; (iii) detecting the polymorphism using a reagent (oligonucleotide primers); and human subjects.

Official Action at page 3 (citations omitted).

After careful consideration of the rejection and the Patent Office's basis for the rejection, applicants respectfully traverse the rejection and offer the following comments.

Jonsson appears to disclose the analysis of "an exonic silent RFLP (G1287A) in the NET gene" as described in Stober *et al.* (1996, *Am J Med Genetics* 67:523-32; hereinafter "Stober"; disclosed in the attached IDS). Jonsson at page 3. Applicants respectfully submit that close consideration of Jonsson and Stober indicates that Jonsson does not disclose every element of the presently claimed invention as recited in claim 1, and thus does not support an anticipation rejection of claims 1, 3, 6-7, 13, and 17. In particular, Jonsson does not teach a polymorphism of a NE transporter gene in a biological sample from the subject, the presence of the polymorphism indicating the susceptibility of the subject to sub-optimal norepinephrine transport.

Contrary to the Patent Office's contention, Jonsson clearly indicates that the polymorphism in the NET gene that they studied is a silent RFLP, meaning that the nucleic acid change G1287A does not result in any amino acid change in the NET polypeptide. This fact is confirmed by referencing Stober, which clearly indicates in Table III on page 526 that G1287A does not produce a variant protein. One of the elements recited in claim 1 (and, by dependence, in claims 3, 6-7, 13, and 17) is the relationship between the presence of a polymorphism and susceptibility to sub-optimal norepinephrine (NE) transport. Since the genomes of subjects bearing the G1287A polymorphism described in Jonsson encode a wild-type NET polypeptide at the polymorphic locus, a relationship between the polymorphism and altered NE transport is not disclosed.

Applicants respectfully submit that given the aforementioned deficiency in the Jonsson reference, Jonsson cannot be held to anticipate the present invention. Accordingly, applicants respectfully request that the rejection of claims 1, 3, 6-7, 13, and 17 under 35 U.S.C. § 102(b) be withdrawn and the claims be allowed at this time.

IV. *Claim Rejections under 35 U.S.C. § 103(a)*

IV.A. *Rejection of Claim 2 over Jonsson in view of Jacob*

Claim 2 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Jonsson in view of Jacob et al. (Circulation, Vol. 99, pp. 1706-12, 1999; hereinafter “Jacob”). The Patent Office’s contentions regarding the Jonsson disclosure have been discussed herein above. The Patent Office concedes, furthermore, that Jonsson does not teach the correlation of sub-optimal NE transport to orthostatic intolerance (OI). Official Action at page 4. According to the Patent Office, however, Jacob teaches a method of detecting sub-optimal norepinephrine in a biological sample as an indication of susceptibility to NE transport. The Patent Office therefore asserts that:

it would have been prima facie obvious to a person of one of ordinary skill in the art at the time the invention was made, to combine a method of detecting polymorphism in NE transporter as taught by Jonsson et al. with determining abnormal norepinephrine clearance in orthostatic intolerance as taught by Jacob et al. to achieve expected advantage of developing a sensitive method for detecting susceptibility of a subject to orthostatic intolerance (OI) because Jacob et al. suggests that “impairment in the norepinephrine transporter could be responsible for the decreased norepinephrine spillover observed in OI patients and the role of norepinephrine transporter function in the dramatic abnormalities in catecholamine clearance must receive increased attention.”

Official Action at pages 4-5. Further, according to the Patent Office:

An ordinary practitioner would have been motivated to combine the method of Jonsson et al. with the method of Jacob et al. to improve sensitivity of the assay by incorporating additional parameters (such as correlating the polymorphism in NE transporter gene to susceptibility to OI) because this limitation would improve analysis, which would result in a better detection of orthostatic intolerance in human subjects.

Official Action at page 5.

After careful consideration of the rejections, applicants respectfully traverse the rejections and submit the following comments.

Preliminarily, applicants note that the U.S. Court of Appeals for the Federal Circuit (C.A.F.C.) has set forth in Environmental Design Ltd. v. Union Oil Co., 713 F.2d 693 (Fed. Cir. 1983), cert. denied, 464 U.S. 1043 (1984), that the factual determinations to be made, as well as the evidence to consider, in making an obviousness determination under §103 include:

- a) the scope and content of the prior art;
- b) the differences between the prior art and the claimed invention;
- c) the level of ordinary skill in the pertinent art; and
- d) additional evidence, which may serve as indicia of non-obviousness.

All relevant evidence on each of these four dispositive issues must be fully considered and evaluated to determine whether the claimed invention would have been obvious. Additionally, it is well known that for an obviousness-type rejection to stand, the cited document or combination must disclose all aspects of the claimed invention; contain a suggestion to modify the cited document(s) to arrive at the claimed invention; and there must be a reasonable chance of success.

In Hodosh v. Block Drug Co., 786 F.2d 1136 (Fed. Cir. 1986), the U.S. Court of Appeals for the Federal Circuit set forth what is described as the "tenets of patent law that must be adhered to when applying §103", Id. at 1143, n.5. Those tenets set out in Hodosh are:

- a) the claimed invention must be considered as a whole;
- b) the references must be considered as a whole and suggest the desirability and thus obviousness of making the combination;
- (c) the references must be reviewed without benefit of hindsight vision afforded by the claimed invention; and
- (d) "ought to be tried" is not the standard with which obviousness is determined.

Applicants respectfully submit that Jonsson in view of Jacob does not meet the requirements for a *prima facie* case of obviousness.

Initially, applicants respectfully refer to the above discussion of Jonsson, in which it is shown that Jonsson fails to teach a polymorphism associated with altered NE transport. This deficiency is not cured by the Jacob reference, which does not discuss genetic polymorphism at all. As a result, Jonsson in combination with Jacob fail to teach each and every element of the claimed invention, namely the presence of a polymorphism in the NET gene indicative of the susceptibility of the subject to sub-optimal norepinephrine transport further characterized as susceptibility to orthostatic intolerance as claimed in claim 2. Since the cited combination does not teach each and every element of the claimed invention, applicants respectfully request the withdrawal of the rejection of claim 2 under 35 U.S.C. § 103(a) as being unpatentable over Jonsson in view of Jacob.

Furthermore, the combination of Jonsson and Jacob presents at best an "ought to be tried" scenario similar to that proscribed in Hodosh v. Block Drug Co. discussed above. Applicants respectfully submit that at best, the cited references are simply an "invitation to experiment" and present an "ought-to-be-tried" situation. As the Federal Circuit stated in Hodosh v. Block Drug Co., "ought to be tried" is not the proper standard for determining obviousness. Applicants respectfully submit, therefore, that the cited references in combination present an "ought-to-be-tried" situation and lack a suggestion to modify the references to arrive at the present invention with a reasonable expectation of success even if the references are combined as proposed by the Patent Office.

Summarily, applicants respectfully submit that the Patent Office has not presented a *prima facie* case of obviousness. As such, applicants submit that claim 2 is in condition for allowance and respectfully request that the rejection of claim 2 under U.S.C. §103(a) be withdrawn and that the claim be allowed at this time.

IV.B. Rejection of Claims 11-12 and 16 over Jonsson in view of Pesonen

Claims 11-12 and 16 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Jonsson in view of Pesonen et al. (U.S. Patent No. 6,013,449; hereinafter “Pesonen”). According to the Patent Office, Jonsson teaches a method for screening for susceptibility to NE transport defects by (a) obtaining a biological sample from a human subject and (b) detecting a polymorphism of a NE transporter in the biological sample from the subject, the presence of the polymorphism being an indication of the susceptibility of the subject to sub-optimal NE transport. Also according to the Patent Office, Jonsson teaches the detection of the polymorphism by PCR amplification of a target nucleic acid. The Patent Office concedes, however, that Jonsson does not teach detection of the polymorphism by dideoxy sequencing. The Patent Office contends that this defect is cured by Pesonen, which the Patent Office asserts teaches a method for detecting a polymorphic allele of the serotonin receptor by amplifying a target nucleic acid by PCR and using dideoxy cycle-sequencing. According to the Patent Office, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine a method of determining a polymorphism as taught by Jonsson with the method of detecting variants by sequencing as taught by Pesonen.

After careful consideration of the rejections, applicants respectfully traverse the rejections and submit the following comments.

For a combination of references to render a claimed invention obvious, the combination must disclose each and every element of the claimed invention. Claims 11-12 and 16 depend directly or indirectly from claim 1, which recites detecting a polymorphism of a NE transporter gene in a biological sample from the subject, the presence of the polymorphism indicating the susceptibility of the subject to sub-optimal norepinephrine transport. As such, claims 11-12 and 16 contain all of the elements of claim 1.

As outlined above, Jonsson does not disclose the detection of a polymorphism that is an indicator of sub-optimal NE transport. The polymorphism in Jonsson encodes the wild-type protein, and thus it is not disclosed that the polymorphism is

associated with sub-optimal NE transport. This defect is not cured by Pesonen, which teaches dideoxy sequencing of a polymorphic allele of an entirely different receptor. Thus, the combination of these two references does not disclose each and every element of claims 11-12 and 16. As a result, applicants respectfully submit that the combination of Jonsson and Pesonen does not support an obviousness rejection of claims 11-12 and 16. Applicants respectfully request that the rejection of claims 11-12 and 16 under 35 U.S.C. § 103(a) as being obvious over Jonsson in view of Pesonen be withdrawn and the claims be allowed at this time.

I.V.C. Rejection of Claims 9-10 over Jonsson in view of Weimer

Claims 9-10 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Jonsson in view of Weimer *et al.* (U.S. Patent No. 6,248,526; hereinafter “Weimer”). According to the Patent Office, Weimer:

teaches a method for detecting a target nucleic acid using labeled primers comprising (a) labeling of first (forward) or second (reverse) primer or both primers; (b) labels include enzymes and enzyme substrates, radioactive atoms, fluorescent dyes, [and] chromophores which may be combined to achieve a desired effect, such as one might label a primer with biotin and detect the presence of the primer with avidin labeled with ¹²⁵I.

Official Action at page 7. From this, the Patent Office asserts that

it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine a method of determining a polymorphism as taught by Jonsson *et al.* with a method of detecting a target nucleic acid using labeled primers as taught by Weimer to achieve expected advantage of developing a sensitive method for detecting site of polymorphism of NE transporter gene in a human subject because Weimer suggests that “the use of labeled primers increases fluorescence signal which is directly proportional to the quantity of amplified DNA”. An ordinary practitioner would have been motivated to combine the method of Jonsson *et al.* with the method of Weimer to improve the sensitivity of the assay by incorporating the labeled primers because this limitation would improve analysis, which would result in a better characterization of the target polymorphism.

Official Action at pages 7-8.

After careful consideration of the rejections, applicants respectfully traverse the rejections and submit the following comments.

As discussed above, for a combination of references to render a claimed invention obvious, the combination must disclose each and every element of the claimed invention. Claims 9 and 10 depend indirectly from claim 1, which recites detecting a polymorphism of a NE transporter gene in a biological sample from the subject, the presence of the polymorphism indicating the susceptibility of the subject to sub-optimal norepinephrine transport. As such, claims 9 and 10 include all of the elements of claim 1.

As outlined above, Jonsson does not disclose the detection of a polymorphism that is an indicator of sub-optimal NE transport. The polymorphism in Jonsson encodes the wild-type protein, and thus Jonsson does not disclose that the polymorphism is associated with sub-optimal NE transport. This defect is not cured by Weimer, which teaches a method of detecting a target nucleic acid using labeled primers. Thus, the combination of these two references does not disclose each and every element of claims 9 and 10. As a result, applicants respectfully submit that the combination of Jonsson and Weimer does not support an obviousness rejection of claims 9 and 10. Applicants respectfully request that the rejection of claims 9-10 under 35 U.S.C. § 103(a) as being obvious over Jonsson in view of Weimer be withdrawn and the claims be allowed at this time.

CONCLUSIONS

In light of the above Amendment and Remarks it is respectfully submitted that the present application is now in proper condition for allowance, and such action is earnestly solicited.

If any minor issues should remain outstanding after the Examiner has had an opportunity to study the Amendment and Remarks, it is respectfully requested that the Examiner telephone the undersigned attorney so that all such matters may be

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resolved and the application placed in condition for allowance without the necessity for another Action and/or Amendment.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiencies or credit any overpayments associated with the filing of this correspondence to Deposit Account Number 50-0426.

Respectfully submitted,
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